

## Unilateral true hermaphrodite with 46,XX/46,XY dispermic chimerism

T I FARAG\*, S A AL-AWADI\*, P TIPPETT†, M EL-SAYED‡, T S SUNDARESHAN\*, S A AL-OTHMAN\*, AND M H EL-BADRAMANY§

\*Kuwait Medical Genetics Centre; †MRC Blood Group Unit, University College London; ‡Pathology Department, Al-Sabah Hospital; and §Psychological Medicine Hospital, Kuwait.

**SUMMARY** A 13 year old female presented with ambiguous external genitalia, right inguinal ovotestis, left ovary, apparently normal Mullerian system, and absent Wolffian system. Cultured lymphocytes showed a 46,XX/46,XY karyotype. Histopathology of the gonads confirmed true hermaphroditism. The presence of two genetically different erythrocyte populations was observed. The findings suggested that the patient is a true hermaphrodite dispermic chimera.

In true hermaphroditism both ovarian tissue, including oocytes, and testicular tissue, including germinal cells or tubules, are present in the same subject. This differs from mixed gonadal dysgenesis with unilateral testis and contralateral dysgenetic ovarian 'streak' tissue or agonadia.<sup>1-7</sup> This is the first well documented report of a true hermaphrodite dispermic chimera in the Arab population.

True hermaphrodites have been represented in art and literature for centuries, but Klebs is usually credited with the first scientific report.<sup>8</sup> In 1959, the first chromosomal abnormality was reported.<sup>9,10</sup> The first dispermic chimera true hermaphrodite with 46,XX/46,XY karyotype and two erythrocyte populations was described in 1962.<sup>11</sup> Almost all XX/XY chimeras are true hermaphrodites, but not all true hermaphrodites are chimeras.<sup>6</sup>

### Case report

The proband was born on 15.8.72 after a term pregnancy to young, consanguineous, Arab parents. The grandparents of the proband were also consanguineous. Ambiguity of the external genitalia was noted by the obstetrician at birth. The child was reared as a female.

At seven years, she was a pleasant, well developed, normal young female. Genital abnormalities included a prominent phallus and glans with a

terminal non-functioning urethral orifice. A separate functioning urethral opening and a small vaginal orifice were present in the vestibule. A small, tender, right sided inguinal swelling was palpable. Both serum electrolytes and urinary 17 ketosteroids were normal.

Metaphase chromosomes were prepared from peripheral blood culture. Both G and Q banding was performed. Karyotype analysis of 100 metaphase spreads revealed two distinct cell lines, 46,XX and 46,XY, in a ratio of 80:20.

Laparotomy showed a left ovary, normal Mullerian system, and absent Wolffian system. A tender right inguinal swelling was removed and a wedge biopsy from the left ovary was taken. Corrective surgery was performed to restore the normal female external genitalia by excising more than an inch of the phallus; clitoroplasty and vaginoplasty were also performed.

Histopathological study of the excised inguinal swelling confirmed the presence of ovotesticular tissue, with a spiral furrow in the middle separating it into two modular areas. One showed testicular elements with infantile tubules, and the second showed ovarian tissue with signs of oogenesis, including primordial, growing, atretic, and cystic follicles (figure). Left gonadal biopsy showed primordial ovarian follicles.

At 12 years she was comprehensively reassessed. Her hormonal profile showed a normal prepubertal female pattern and response. Psychological and psychiatric assessment confirmed her to be a well balanced female of average intelligence and feminine gender identity.

The proband and her father were typed for blood groups ABO, Rh, MNSs, P, Lu, Le, Fy, Jk, Xg, and Co. The mother's blood was not available for study. Two erythrocyte populations were detected by a mixed field agglutination picture when the proband's cells were tested with anti-M, anti-C, and anti-K. The two populations of erythrocytes were separated using anti-M. About 20% of her red cells were agglutinated using anti-M: after separation the agglutinates were 'deagglutinated' by treatment with DTT (dithiothreitol), and both 'deagglutinated' and free cells were phenotyped (table). The major

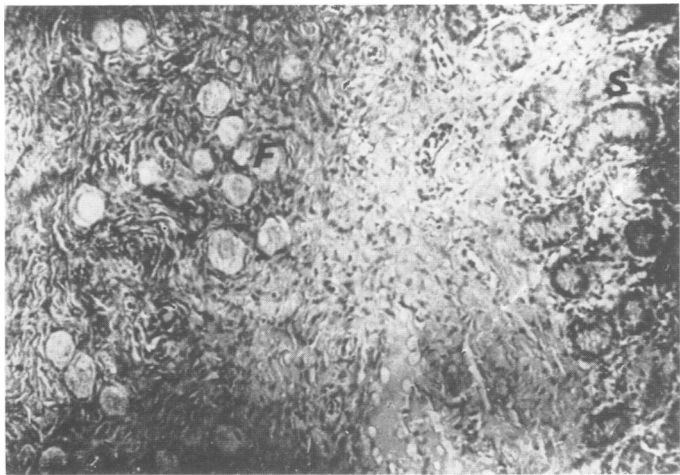


FIGURE Section of the right gonad showing seminiferous tubules (S) and primordial follicles (F).

TABLE Red cell groups of the proband and her father.

	ABO	MN	Rh	K	Fy <sup>a</sup>	Fy <sup>b</sup>
Father	O	N	C+c+D+E-e+	-	-	+
Proband						
Unseparated	A <sub>2</sub>	MN*	C+*c+D+E-e+	+	+	+
Free cells (80%)†	A	N	C+c+D+E-e+	-	+	+
'Deagglutinated' cells (20%)	A	MN	C-c+D+E-e+	+	-	+

All samples were S-s+, P<sub>1</sub>+, Lu(a-), Jk(a+b+), Xg(a+), Co(b-).

\*Mixed field agglutination (see text).

†After separation with anti-M (see text).

population was N, C+, K-, and Fy(a+) and the minority of red cells were MN, C-, K+, and Fy(a-). Two populations of red cells had not been noticed when the unseparated sample was tested with anti-Fy<sup>a</sup>: this failure is not surprising since anti-Fy<sup>a</sup> (not an avid antibody) is used by an antiglobulin technique and it is always more difficult to detect minority populations by this technique unless avid antibodies are used.

Discussion

Twenty-five well documented 46,XX/46,XY true hermaphrodites have been reported. In 1974, 11 cases were reviewed.<sup>12</sup> Subsequently many more cases have been reported.<sup>13-26</sup> Of these only a few cases have been confirmed to be dispermic chimeras (P Tippett, unpublished data).<sup>15 19 27-30</sup> The patient reported here, the first documented dispermic chimera true hermaphrodite in the Arab population, was similar to the first case reported by Gartler *et al*<sup>11</sup> with 46,XX/46,XY karyotype, right ovotestis, and left ovary, reared as a female, arising from two different events of fertilisation by two different sperms with X and Y genotypes.

The possible mechanisms for the formation of gonosomal chimerism were reviewed by Ford<sup>31</sup> who described nine possible mechanisms separated into two groups: chimeras from two separate acts of syngamy and chimeras resulting from two independent zygotes. Three mechanisms for the occurrence of dispermic chimeras in man were reported, including participation of either nuclei of the ovum and second polar body, or of two haploid nuclei and daughter of the ovum nucleus, or due to fusion of one daughter zygote nucleus and nucleus of the second polar body. In 1980, chromosome heteromorphism in chimeras was established.<sup>25</sup>

In this case the red cell groups show that the proband has received two maternal contributions (one gamete carrying M, K, and Fy<sup>b</sup> and the other carrying N, k, and Fy<sup>a</sup>) as well as two paternal contributions (X and Y).

Further information is required to answer questions concerning origin, general phenotype, rearing sex, and development of individual tissues of true hermaphrodites of dispermic origin, including data on blood, immune system, musculoskeletal system, reproductive system, nervous system, and behaviour.

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## References

- <sup>1</sup> Shoval AR. Mixed gonadal dysgenesis. In: Rashad MN, Morton WRM, eds. *Genital anomalies*. Springfield, Illinois: Charles C Thomas, 1969:476-89.
- <sup>2</sup> Jones HWJ, Scott WW. *Hermaphroditism, genital anomalies and related endocrine disorders*. Baltimore: Williams & Wilkins, 1971:290-317.
- <sup>3</sup> Davidoff F, Federman DD. Mixed gonadal dysgenesis. *Pediatrics* 1973;**52**:725-42.
- <sup>4</sup> Simpson JL. *Disorders of sexual differentiation: etiology and clinical delineation*. New York: Academic Press, 1976:237-9.
- <sup>5</sup> Al-Awadi SA, Cuschieri A, Farag TI, et al. Mixed gonadal dysgenesis and sex chromosome mosaicism with multiple cell lines including structural abnormalities of the Y chromosome. *Clin Genet* 1983;**23**:172-6.
- <sup>6</sup> de la Chapelle A. Sex chromosome abnormalities. In: Emery AEH, Rimoin DL, eds. *Principles and practice of medical genetics*. Edinburgh: Churchill Livingstone, 1983:193-215.
- <sup>7</sup> Al-Awadi SA, Farag TI, Naguib KK, et al. A five year experience with gonosomal abnormalities in Kuwait. *J Kwt Med Assoc* 1984;**18**:225-32.
- <sup>8</sup> Klebs E. *Handbuch der Pathologischen Anatomie*. Berlin: Hirschwald, 1876.
- <sup>9</sup> Harnden DG, Armstrong CN. The chromosomes of a true hermaphrodite. *Br Med J* 1959;**ii**:1287.
- <sup>10</sup> Hungerford DS, Donnelly AJ, Nowell PC, Beck S. The chromosome constitution of a human phenotypic intersex. *Am J Hum Genet* 1959;**2**:215-36.
- <sup>11</sup> Gartler SM, Waxman SH, Giblett E. An XX/XY human hermaphrodite resulting from double fertilization. *Proc Natl Acad Sci USA* 1962;**48**:332-5.
- <sup>12</sup> Van Niekerk WA. *True hermaphroditism*. New York: Harper, 1974.
- <sup>13</sup> Manuel MA, Allie A, Jackson WPU. A true hermaphrodite with XX/XY chromosome mosaicism. *S Afr Med J* 1965;**39**:414-9.
- <sup>14</sup> Massimo L, Vianello MG. Chromosome studies in two cases of intersexuality. *Human Chromosome Newsletter* 1965;**15**:15-16.
- <sup>15</sup> Race RR, Sanger R. *Blood groups in man*. 6th ed. Oxford: Blackwell, 1975:531-9.
- <sup>16</sup> Fitzgerald PH, Brehaut LA, Shannan FT, Angus HE. Evidence of XX/XY sex chromosome mosaicism in a child with true hermaphroditism. *J Med Genet* 1970;**7**:383-8.
- <sup>17</sup> Park JJ, Jones HW Jr, Bias WG. True hermaphroditism with ambiguous external genitalia. *Am J Obstet Gynecol* 1970;**108**:1197-205.
- <sup>18</sup> Kakati S, Sharma T, Udupa KN, Chaudhuri SPR. A true hermaphrodite with XX/XY mosaicism. *Ind J Med Res* 1971;**59**:104-6.
- <sup>19</sup> Benirschke K, Naftalin F, Gittes R, Khuder G, Yen SSC, Allen FH. True hermaphroditism and chimerism. *Am J Obstet Gynecol* 1972;**113**:449-58.
- <sup>20</sup> Grace JH. A white hermaphrodite in South Africa. *S Afr Med J* 1973;**47**:1553-4.
- <sup>21</sup> Shanfield I, Young RB, Hume DM. True hermaphroditism with XX/XY mosaicism: report of a case. *J Pediatr* 1973;**83**:471-3.
- <sup>22</sup> de la Chapelle A, Schröder J, Rantanen P, et al. Early fusion of two human embryos. *Ann Hum Genet* 1974;**38**:63-75.
- <sup>23</sup> De Marchi M, Carbonara AO, Carozzi F, et al. True hermaphroditism with XX/XY chromosome mosaicism: report of a case. *Clin Genet* 1976;**10**:265-72.
- <sup>24</sup> Fitzgerald PH, Donald RA, Kirk RL. A true hermaphrodite dispermic chimera with 46,XX and 46,XY karyotypes. *Clin Genet* 1979;**15**:89-96.
- <sup>25</sup> Dewald G, Haymond MW, Spurbeck JL. Origin of 46,XX/46,XY chimerism in a human true hermaphrodite. *Science* 1980;**207**:321-3.
- <sup>26</sup> Shah VC, Krishna Murthy DS, Sabita Roy, Contractor PM, Shah VA. True hermaphrodite 46,XX/46,XY: clinical, cytogenetic and histopathological studies. *Ind J Pediatr* 1982;**49**:885-90.
- <sup>27</sup> Borgaonkar DS. *Chromosomal variation in man. A catalog of chromosomal variants and anomalies*. 3rd ed. New York: Alan R Liss, 1980:483-5.
- <sup>28</sup> de Grouchy J, Turleau C. *Clinical atlas of human chromosomes*. 2nd ed. New York: John Wiley, 1984:406-8.
- <sup>29</sup> Schinzel A. *Catalogue of unbalanced chromosome aberrations in man*. Berlin: Walter de Gruyter, 1984:812-3.
- <sup>30</sup> Tippet P. Human chimeras. In: *Chimeras in developmental biology*. London: Academic Press, 1984:165-78.
- <sup>31</sup> Ford CE. Mosaicism and chimeras. *Br Med Bull* 1969;**25**:104-9.

Correspondence and requests for reprints to Dr Patricia Tippet, MRC Blood Group Unit, Wolfson House, University College London, 4 Stephenson Way, London NW1 2HE.

## Interstitial del(13)(q21·3q31) associated with psychomotor retardation, eczema, and absent suck and swallowing reflex

P J PEET, R RODRIGUES PEREIRA, J O VAN HEMEL, AND A J M HOOGEBOOM

Department of Paediatrics, St Clara Hospital, and Department of Clinical Genetics, Erasmus University, Rotterdam, The Netherlands.

**SUMMARY** A patient with a deletion (13)(q21·3q31) showed only eczema and ab-

sent suck and swallowing reflex, in contrast to other well documented cases with a similar deletion. Apparently there is wide clinical variability in patients with deletions in this area.